

Bortezomib Maintenance Therapy- 14 dayⁱ

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Maintenance treatment for patients with high risk multiple myeloma	C90	00435a	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.

Bortezomib is administered once every 14 days for 2 years or until disease progression or unacceptable toxicity occurs.

Day	Drug	Dose	Route	Cycle
1	Bortezomib	1.3mg/m ²	^{a,b} SC (abdomen or thigh)	Every 14 days
^a Note: In individual cases where approved by consultant, bortezomib may be administered as IV bolus over 3-5 seconds through a peripheral or central intravenous catheter followed by a flush with 0.9% NaCl. Note the concentration of bortezomib solution should be 1mg/ml when administered via the IV route				
^b The solution should be injected subcutaneously, at a 45-90° angle. Injection sites should be rotated for successive injections. If local injection site reactions occur, either a less concentrated solution may be administered sc or a switch to intravenous injection is recommended.				
Bortezomib is a proteasome inhibitor and is neurotoxic. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer. Here				

ELIGIBILITY:

- Indications as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to bortezomib, boron or any of the excipients
- Pregnancy

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal, liver and bone profile.
- Blood pressure, blood glucose (patients on oral hypoglycaemics).
- Virology screen -Hepatitis B (HBsAg, HBcoreAb) & C, HIV ***See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation**

NCCP Regimen: Bortezomib Maintenance Therapy-14 day	Published: 30/10/2018 Review: 12/05/2026	Version number: 2
Tumour Group: Myeloma NCCP Regimen Code: 00435	IHS Contributor: Prof Ezzat Elhassadi	Page 1 of 5
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Regular tests:

- FBC; monitor platelet count **at a minimum** of day 1 and day 8 each cycle,
- Renal, liver and bone profile
- Blood pressure, *blood glucose if being treated with oral hypoglycaemics. (* See Drug Interactions)

Disease monitoring:

Disease monitoring should be in line with the patient’s treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Bortezomib therapy should be withheld when the platelet count is $< 25 \times 10^9 /L$

Haematological:

Table 1: Dose modification of bortezomib based on haematological toxicity

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Bortezomib Dose
≥ 0.5	and	≥ 30	100% dose
< 0.5	or	<30	Consider delay until recovery checking FBC weekly; reduce dose to 1.0 mg/m ²
Reoccurrence of < 0.5	or	Reoccurrence of < 30	Consider delay until recovery checking FBC weekly; further reduce dose to 0.7 mg/m ²

Renal and Hepatic Impairment:

Table 2: Recommended dose modification for renal or hepatic impairment

Bortezomib		Grade of Hepatic Impairment*	Bilirubin Level**	(AST) Levels**	Modification of starting dose
It is unknown if the pharmacokinetics of bortezomib are influenced in patients with severe renal impairment not undergoing dialysis (CrCL < 20ml/min). Since dialysis may reduce bortezomib concentrations, it should be administered after the dialysis procedure		Mild	≤1 x ULN	> ULN	None
			>1-1.5xULN	Any	None
		Moderate	>1.5-3xULN	Any	Reduce dose to 0.7mg/m ² in the first treatment cycle. Consider dose escalation to 1mg/m ² or further dose reduction to 0.5mg/m ² in subsequent cycles based on patient tolerability.
		Severe	>3xULN	Any	

*Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe)

**ULN = Upper Limit Normal

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Neuropathic pain and/or peripheral neuropathy:

Table 3: Recommended dose modifications for bortezomib-related neuropathy

Severity of neuropathy	Dose Modification
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) with no pain or loss of function	None
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL))	Reduce dose to 1 mg/m ²
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL)	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment and reduce dose to 0.7mg/m ²
Grade 4 (life-threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy	Discontinue treatment

Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

Dose reductions for other toxicities:

Table 4: Dose modification schedule of bortezomib based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
Grade ≥ 3 Non-haematological toxicity		.Withhold treatment until symptoms of the toxicity have resolved. Treatment may be re-initiated at a 25% reduced dose (1.3mg/m ² reduced to 1.0mg./m ² ; 1.0mg/m ² reduced to 0.7mg/m ²). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk
New or worsening pulmonary symptoms (e.g. cough, dyspnoea)		Withhold treatment. Prompt diagnostic evaluation required and benefit/risk ratio should be considered prior to continuing bortezomib therapy.
Posterior Reversible Encephalopathy Syndrome (PRES)	Discontinue bortezomib	

*Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low (Refer to local policy).

PREMEDICATIONS: Not usually required. Ensure patient remains well hydrated during treatment

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OTHER SUPPORTIVE CARE:

- Bisphosphonates should be considered in all patients with myeloma related bone disease.
- Consider the use of a H₂ antagonist or proton pump inhibitor if appropriate in patients receiving dexamethasone therapy (**Refer to local policy**).
- Consider PJP prophylaxis (**Refer to local policy**).
- Consider low dose anti-viral prophylaxis (**Refer to local policy**).

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Bortezomib

- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. (**Refer to local infectious disease policy**). These patients should be considered for assessment by hepatology.
- **Peripheral Neuropathy:** Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.
- **Hypotension:** Treatment is commonly associated with orthostatic/postural hypotension. A minority of patients with orthostatic hypotension experienced syncopal events.
- **Hepatic Impairment:** Bortezomib is metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with bortezomib at reduced doses and closely monitored for toxicities.
- **Haematological toxicity:** Gastrointestinal and intracerebral haemorrhage have been reported in association with bortezomib treatment. Therefore platelet counts should be monitored prior to each dose of bortezomib and bortezomib should be withheld when the platelet count is < 25x 10⁹cells/L. Potential benefit of treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding. Platelet transfusion should be considered when clinically appropriate.
- **Gastrointestinal toxicity:** Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are very common with bortezomib treatment.
- **Seizures:** Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.
- **Posterior Reversible Encephalopathy Syndrome (PRES):** In patients developing PRES, treatment with bortezomib should be discontinued.
- **Heart Failure:** Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Patients with risk factors for or existing heart disease should be closely monitored.

DRUG INTERACTIONS:

- Additive hypotensive effect with antihypertensives and bortezomib. Blood pressure should be monitored and ensure patient is well hydrated prior to bortezomib dose. Adjustment of antihypertensives may be required.
- During clinical trials, hypoglycemia was uncommonly reported and hyperglycemia commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics

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- Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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2. Sonneveld P, Schmidt-Wolf IG et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. *J Clin Oncol.* 2012;30(24):2946.
3. VELCADE[®] Summary of Product Characteristics Accessed March 2021. Available at https://www.ema.europa.eu/en/documents/product-information/velcade-epar-product-information_en.pdf
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at: <https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf>

Version	Date	Amendment	Approved By
1	10/10/2018		Dr. Ezzat Elhassadi
2	12/05/2021	Regimen review Updated wording regarding management of hepatitis B reactivation	Prof. Ezzat Elhassadi

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

ⁱ This is an unlicensed indication for the use of Bortezomib[®] in Ireland. Patient's should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.

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Tumour Group: Myeloma NCCP Regimen Code: 00435	IHS Contributor: Prof Ezzat Elhassadi	Page 5 of 5
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